Drug related safety issues affecting pregnancy outcome and concerning risk minimisation measures

Crijns, Hubertina Johanna Maria Josephina

Chapter 4

Situation in the Netherlands regarding isotretinoin

1) Healthcare professional surveys to investigate the implementation of the isotretinoin Pregnancy Prevention Programme - A descriptive study.
2) Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study.
3) Pregnancies in the Netherlands (TIS)

- 67% of the patients heard about the isotretinoin PPP from their treating physician.
- 6% of the patients used isotretinoin for mild acne instead of moderate to severe acne.
- 61% of the patients had a pregnancy test before starting isotretinoin treatment. 33% performs pregnancy tests on a monthly basis.
- 11% of the pharmacists did ask for pregnancy test results.
- 61% of the patients receives prescriptions covering one month treatment and 33% received prescriptions for three months.
- 72% of responding patients uses contraceptive measures, the remaining patients were not sexually active. 17% did not use contraceptive measures with every sexual contact.
- 50% of the patients considers the PPP a mutual responsibility of prescriber and patient.

Results patient survey (*n*=18)

Chapter 4.1

Healthcare professional surveys to investigate the implementation of the isotretinoin Pregnancy Prevention Programme A descriptive study

Ineke Crijns[1,2], Aukje Mantel-Teeuwisse[3], Rudi Bloemberg[1], Eldridge Pinas[2], Sabine Straus[2,4], Lolkje de Jong-van den Berg[1]

1) University of Groningen, Department of PharmacoEpidemiology & PharmacoEconomics, Research Institute for Health Research (SHARE), Groningen, the Netherlands
2) Medicines Evaluation Board, Utrecht, the Netherlands
3) Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, the Netherlands
4) Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands

Resubmitted after adjustment

ABSTRACT

Background

The current EU isotretinoin Pregnancy Prevention Programme (PPP) has been implemented in 2003-2004, but pregnancies still occur. Health care professionals are involved in the execution of this PPP and have an important role.

Objective

The aim of conducting these three surveys was to explore the compliance with the PPP by community pharmacists and dermatologists, in the Netherlands. The two surveys among pharmacists have been conducted in 2007 and 2011, allowing us to assess improvement over time.

Methods

Three online questionnaires related to adherence to the PPP of isotretinoin were performed. Two surveys were sent to pharmacists. In 2007, a survey was sent to approximately 1000 pharmacies who are member of the Utrecht Pharmacy Panel for Education & Research (UPPER) network. In 2011, the second survey was sent the Dutch Association of Pharmacists (KNMP), especially the specific research group of the Association (*n*=556 pharmacists). In 2010, a survey was sent to 564 practicing dermatologists and dermatologists in training registered to the Dutch Association of Dermatology and Venereology (NVDV).

Results

Both pharmacists questionnaires had response rates of 20% and the dermatologist questionnaire had a response rate of 28%.

Dispensing checks on the limitation of 30 days' supply for isotretinoin by pharmacists remained stable (82%) over the years. The seven day validity of the prescription check decreased from 61% to 53%. Only 15% of the pharmacists asked the patient for a negative pregnancy test before each dispensing, and the use of contraception was checked before each dispensing by 44-49% of the pharmacists, which remained stable over time.

The majority of the pharmacists (72-74%) considered that the main responsibility for the isotretinoin PPP lies with the prescriber.

Contraception will be prescribed by 105 dermatologists (64%); in addition 35 dermatologists (22%) prescribe contraceptives after checking whether the patient is already on contraception or refer these patients to a gynaecologist or general practioner for contraception.

93% of the dermatologists were of the opinion that he/she performed the PPP. Analysis of the response on adherence to the different elements of the PPP showed however that 41 (25%) were compliant with the PPP.

Conclusions

The observed non-adherence to the isotretinoin PPP calls for careful evaluation of proposed risk minimisation plans and participation of all stakeholders in the developmental phase of these plans.

INTRODUCTION

The thalidomide disaster in 1961-1962 revealed that drugs thought to be relatively safe may disguise a serious risk. This catastrophe increased the awareness of potential adverse reactions to drug exposure, but also the awareness of pharmacovigilance during pregnancy or otherwise. Besides developing systems to collect spontaneous adverse reaction reports due to drug exposure and collecting data for pharmaco-epidemiology drug utilisation studies, a more pro-active approach on managing risks has been established, including taking risk minimisation measures, such as a pregnancy prevention programme [1].

Vitamin A derivates are known to be teratogenic. Isotretinoin, a vitamin A derivative has been licensed for the treatment of acne since 1982 in the USA and 1984 in Europe. Despite the fact that the product information of isotretinoin (Roaccutane®, Roche) contained a contra-indication for pregnancy at the time of approval, exposure during pregnancy occurred and congenital anomalies have been reported, even if isotretinoin had been taking for short periods of time [2,3]. In 1985 the isotretinoin embryopathy has been first described by Lammer *et al* [4]. This embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects and has a frequency of 26% in exposed patients. In 1988, in order to improve the prevention of pregnancies, Roche introduced a Pregnancy Prevention Programme (PPP) worldwide [5]. Key principles of the isotretinoin PPP are educational material for health care providers and patients, therapy management and dispensing control.

In 2003, generic formulations of isotretinoin entered the European market. In the European Union (EU) a review [6] was performed and the European Commission (EC) decided that an EU PPP should be applicable to all isotretinoin containing products for systemic use. In the current EU PPP, prescribers, pharmacists, and patients are involved to perform this PPP appropriately. This PPP was implemented in most EU countries [7]. See Box 1 for all elements of the current EU PPP.

Box 1, Elements of the current EU PPP

- Contra-indication pregnant women and females of childbearing potential
- Pregnancy tests before, during and after discontinuation
- Two methods of contraception
- Educational material physician
- Educational material pharmacist
- Information patient
- Patient information on contraceptive methods
- Informed consent form
- Restricted supply females of childbearing potential, for 30 days and prescription validity of 7 days

Despite of the existence of the PPP, pregnancies still occur in both the US [8] and Europe [9] and congenital anomalies due to in utero exposure to isotretinoin are still reported.

Pro-active risk minimisation programmes such as the isotretinoin PPP have been developed to prevent undue harm to patients. Their effectiveness in daily medical practice largely depends on actual adherence of all stakeholders to these programmes. Patients' compliance has been assessed with regard to adherence of contraception requirements in several studies [8,10,11]. Limited information, however, is available on compliance with the current isotretinoin PPP recommendations by pharmacists [12,13] and dermatologists [12]. Therefore, we conducted three surveys among health care professionals and the aim of these surveys was to explore the compliance with the isotretinoin PPP by community pharmacists and dermatologists, in the Netherlands. The two surveys among pharmacists have been conducted in 2007 and 2011, allowing us to assess improvements over time. The second pharmacist survey and the dermatologist survey are part of an investigational programme because of the results of the first pharmacist survey.

MATERIAL AND METHODS

Data collection

Three surveys were performed, two among pharmacists and one among dermatologists.

UPPER network

In 2007, a short online questionnaire was developed and the link was sent once (April 16, 2007) to approximately 1000 pharmacies who are member of the Utrecht Pharmacy Panel for Education & Research (UPPER) network of the Department of Pharmaceutical Sciences, Utrecht University, the Netherlands. The questionnaire was closed after 2 weeks, because the number of completed questionnaires was higher than anticipated for this pilot study. The structured questionnaire contained a combination of 14 closed and open questions. The questions addressed apart from general issues, more specific items as checks on dispensing, therapy management, perceived responsibility and role of the pharmacist.

Dutch Association of Pharmacists

In 2011, it was decided to repeat the 2007 survey among pharmacists and the questionnaire was amended based on the questionnaire of the UPPER network and consisted of 22 questions. The link to this questionnaire was originally included in a Newsletter of the Dutch Association of Pharmacists, but because of a low response, the link to the questionnaire was sent in addition to the specific research group of the Association (n=556 pharmacists) by e-mail on April 1, 2011. After three weeks a reminder was sent. The collection period covered 3 month period from 1 April 2011 through 1 July 2011.

Duplicates and incomplete questionnaires have been excluded from the analyses.

Fully compliance with the Isotretinoin PPP for pharmacists consists of adherence to dispensing control (dispensing for 30 days, prescription validity of 7 days), provision of educational material and check of availability of negative pregnancy testing and use of contraception at time of every dispensing of isotretinoin to women of childbearing potential.

Dermatologists
In 2010, a questionnaire was developed consisting of eight questions aimed at dermatologists. An e-mail with a link to the online version was sent to 564 practicing dermatologists and dermatologists in training registered with the Dutch Association of Dermatology and Venereology (NVDV). A reminder was sent once, after six weeks. The response was collected over the period of May 2010 through September 2010. The questions concerned those parts in the PPP dealing with information provision to patients, actions of prescribers and their interaction with patients.

Statistics
Descriptive statistics were performed on the data collected by the questionnaires.

RESULTS

Pharmacist questionnaires 2007 and 2011
A total of 208 pharmacists participated in the 2007 survey, a response rate of 20%. In most of the pharmacies (69%) less than five patients filled prescriptions for isotretinoin at time of the survey.

A total of 155 questionnaires were filled in the three month period in 2011. Eliminating duplicates and incomplete filled responses, 148 questionnaires were included in the analyses consisting of reactions on the Newsletter and the Association research group. Only the response rate of the research group could be determined, because the source population of the Newsletter could not be determined. The response rate of the research group was 20%, 109 out of 556 pharmacists.

Table 1 Results on responses by both pharmacists' surveys and the dermatologist survey

	UPPER Network 2007 *N*=208 (%)	Dutch Association of Pharmacists 2011 *N*=148 (%)	Dermatologists 2010 *N*=161 (%)
General			
Number of patients on isotretinoin at time of the survey			
- <5	143 (68.8)	76 (51.4)	
- 5-10	50 (24.0)	54 (36.5)	
- 11-20	12 (5.8)	12 (8.1)	
- >20	3 (1.4)	6 (4.1)	
Are you aware of a Pregnancy Prevention Programme for isotretinoin?			
- Yes	163 (78.3)	150 (95.5)	152 (94,4)
- No	18 (8.7)	7 (4.5)	9(5.6)
- Missing	27 (13.0)		
Distribution control			
From which prescribers do you accept a prescription for isotretinoin?			
- Dermatologist	70 (33.7)	48 (32.4)	
- Dermatologists, GP and/or gynaecologist	44 (21.6)	42 (28.4)	
- All physicians	86 (41.3)	60 (38.5)	
Does your pharmacy system provide an alert on the maximum of 30 days per prescription?			
- Yes	172 (82.7)	121 (81.8)	
- No	25 (12.0)	27 (18.2)	
- Missing	11 (5.3)		
Do you deviate from this rule?			
- Never	71 (34.1)	53 (35.8)	80 (49.7)
- Rarely	38 (18.3)	46 (31.1)	61 (37.9)
- Regularly	37 (17.8)	6 (4.1)	
- Only in exceptional circumstances	43 (20.7)	43 (29.1)	
- Missing	19 (9.1)	8 (5.1)	3 (1.9)
Do you check the tenability of 7 days for a prescription of isotretinoin?			
- Yes	127 (61.1)	79 (53.4)	
- No	66 (31.7)	25 (16.9)	
- Only in exceptional circumstances		44 (29.7)	
- Missing	15 (7.2)		

Table 1 Results on responses by both pharmacists' surveys and the dermatologist survey

	UPPER Network 2007 *N*=208 (%)	Dutch Association of Pharmacists 2011 *N*=148 (%)	Dermatologists 2010 *N*=161 (%)
Providing information			
To whom do you provide information regarding the PPP of isotretinoin?			
- All patients	45 (21.6)	34 (23.0)	
- Women of childbearing potential	121 (58.2)	91 (61.5)	
- Others	9 (4.3)	2 (1.4)	
- No additional information will be provided	22 (10.6)	21 (14.2)	
- Missing	11 (5.3)		
Which brochures will be provided?			
On isotretinoin			
- Yes	163 (78.4)	127 (85.8)	
- No	45 (21.6)	21 (14.2)	
On contraceptive methods			
- Yes	81 (38.9)	107 (72.3)	
- No	127 (61.1)	41 (27.7)	
Other information			
- Yes	3 (1.5)	107 (72.3)	
- No	205 (98.5)	41 (27.7)	
Additional oral information?			
- Yes	120 (57.7)	97 (65.5)	
- No	29 (13.9)	39 (26.4)	
- Missing	59 (28.4)	1 (0.7)	
Pregnancy Prevention Programme			
Who is responsible for the PPP?	150 (72.1)	110 (74.3)	4 (2.5)
- Prescriber	11 (7.3)	10 (6.8)	
• Specific arrangements	139	100	
• No specific arrangements	(92.7)	(67.6)	
- Pharmacist			

Table 1 Results on responses by both pharmacists' surveys and the dermatologist survey

	UPPER Network 2007 *N*=208 (%)	Dutch Association of Pharmacists 2011 *N*=148 (%)	Dermatologists 2010 *N*=161 (%)
- Patient	9 (4.3)	9 (6.1)	40
- Otherwise	10 (4.8)	11 (7.4)	(24.8)
• Combination prescriber and pharmacist	25 (12.0)	18 (12.2)	
• Combination prescriber and patient	14 (56.0)		NA**
• Combination prescriber, pharmacists and patient	4 (16.0)		117
• Regulatory authority and pharmaceutical industry	6 (24.0)		(72.7)
- Missing	1 (4.0)		NA
	14 (6.7)		NA
Do you check the following?:			
Negative pregnancy test			
- First dispensing / prescription	27 (13.0)	32 (21.6)	145
- Each dispensing / prescription	32 (15.4)	23 (15.5)	(90.0)
- Never	106 (51.0)	92 (62.2)	104
- Missing	43 (20.7)	1 (0.7)	(64.6)
			12
Contraceptive use			(7.5)
- First dispensing / prescription	43 (20.7)	50 (33.8)	3 (1.9)
- Each dispensing / prescription	91 (43.8)	72 (48.6)	
- Never	41 (19.7)	26 (17.6)	
- Missing	33 (15.9)		105
			(65.2)/
			140
			(87.0)*
Has the pharmacist a surveillance function regarding the PPP?			
- Yes	132 (63.5)	103 (69.6)	
- No	56 (26.9)	26 (17.6)	
- Missing	20 (9.6)	19 (12.8)	
		'otherwise'	

* Contraception will be prescribed by 105 responders (65%), but including those who first check before prescribing or refer patients to a gynaecologist or GP it will be 140 responders (87%)
** NA = Not Applicable

In 2011, of the responding pharmacists 61% (*n*=90) were female and 39% (*n*=58) were male pharmacists. 39% of all pharmacists (*n*=57) belonged to the age group of 23-35 years of age, 29 % (*n*=43) to the age group 35-45 years of age, 23% (*n*=34) to the age group 45-55 years of age and 9% (*n*=14) to the age group 55-65 years of age. Hundred forty-three (97%) pharmacists were working in a community pharmacy. The majority of the responders, 51% (*n*=76), had less than 5 patients filling prescriptions for isotretinoin.

In 2007, 78% of the pharmacists confirmed that they were aware of the isotretinoin PPP compared with 96% of the responders in 2011, see Table 1.

Dispensing
Approximately one third of all pharmacists (32-34%) accepted prescriptions from dermatologists only. Most pharmacists (90% in 2007, 84% in 2011) dispensed generic forms of isotretinoin only. Results are presented in Table 1.

Dispensing checks
In both surveys the 82-83% of the pharmacists indicated that they receive a computer alert reminding them that the prescription of isotretinoin should be limited to a 30 day supply for all female patients at risk of pregnancy. Only 35% never deviated from this rule. Main reasons mentioned for deviation from the requirement were patients' holidays, physicians' requests and unintended ignorance of the computer alert. The seven day validity of the isotretinoin prescriptions was adhered to by 61% in 2007 compared to 53% in 2011.

Therapy management
Both surveys reported that approximately 10% did not provide any information on the isotretinoin PPP to women of child bearing potential. Information on contraception was more frequently provided in 2011 than in 2007 (85.8% and 38.9%, respectively). Only 15-16% of the pharmacists mentioned asking for a negative pregnancy test result before each dispensing of isotretinoin to women of childbearing potential, whereas more than half of the pharmacists stated that they never asked for test results. The use of contraception was checked at time of every dispensing by 44-49%, at time of first dispensing only by additional 20.7% in 2007, but in 2011 the Association pharmacists an additional 33.8% checked contraception with first dispensing.

Perceived responsibility and role of the pharmacist
With both surveys, the majority of pharmacists (72-74%) considered that the main responsibility for the isotretinoin PPP lies with the prescribers. Others considered a combination of prescriber and either pharmacist or patient or all of them primarily responsible for the programme. On the other hand, 63.5% of the pharmacists in 2007 agreed they should play a role in monitoring the isotretinoin PPP in the surveillance or otherwise, which was even higher in 2011 (82.4%).

Adherence to the dispensing control
In both surveys, only a limited number of pharmacists, 6.7% in 2007 and 8.8% in 2011, fully complied with all aspects of the isotretinoin PPP. Pharmacists complying with all aspects of the dispensing control element that is part of the isotretinoin PPP consisted of 39% in both groups.

Potential enhancers of adherence

In 2011, pharmacists were asked for suggestions to increase the compliance with the PPP. Suggestions received were: oblige prescriber to prescribe contraceptives together with drugs like isotretinoin, better communication, better information tools, informed consent form for patients to be signed at the pharmacy, to improve the pharmacy monitoring systems, to have stickers with warnings for drugs like isotretinoin and unambiguous policy on responsibility of the individual stakeholders of such programmes.

Dermatologists

Hundred-sixty one out of the 564 surveyed dermatologists and dermatologists in training completed the questionnaire, a response rate of 28.5%.

Responders were aware of the PPP of isotretinoin through their professional association in 35%, followed by the pharmaceutical industry (12%), literature (4%) or the product information of isotretinoin (2%), see Table 1. Most of the responders received the information through a combination of the different sources. Nine dermatologists (6%) indicated not to be aware of the PPP.

Hundred-fifteen (71%) of the responders agreed with the need for a PPP for isotretinoin. Reasons for disagreement were that the PPP was too strict (*n*=10), patronising (*n*=9), unnecessary (*n*=6), no difference compared to other products with a contraindication for use during pregnancy (*n*=6), responsibility of the patient after providing information (*n*=5), time consuming (*n*=2) and single arguments such as it will cause concerns, cause an unnecessary threshold, there is no 100% guarantee, too interfering, too many exceptions and too general.

According to 117 responders (72.7%), the responsibility for pregnancy prevention should be a shared responsibility by both prescriber and patient. Forty responders (24.8%) considered the patient solely responsible for the adherence to the PPP. Four responders considered it completely their responsibility (2.5%).

Table 2: Opinion about execution of PPP by dermatologists as a whole and about separate elements of PPP (*n*=161)

Question	Always n (%)	Sometimes n (%)	Never n (%)	Missing n (%)
Execution PPP	150 (93)	- (0)	8 (5)	2 (1)
Signing informed consent form	112 (70)	31 (19)	15 (9)	2 (1)
Performance of pregnancy tests	104 (65)	41 (25)	12 (7)	3 (2)
Monthly prescriptions	80 (50)	61 (38)	16 (10)	3 (2)
Regular prescriptions contraceptive	83 (52)	65 (40)	9 (6)	3 (2)

Time needed to inform the patient and performing the other PPP elements for prescribers took the responders mostly 5 minutes (35%), or less (34%). Three responders mentioned that either a nurse or a physician assistant performed these tasks.

Hundred-five responders (65%) also prescribed contraceptives. In addition, 35 dermatologists (22%) mentioned that they prescribed contraceptives after checking whether the patient is already on contraception or refer patients to a gynaecologist or general practioner for contraception. Ten responders (6.2%) mentioned that they would not prescribe a contraceptive for patients indicating to be not sexually active, for instance in case of religious reasons. Furthermore, ten responders (6.2%) informed the patient about the risks but stated that pregnancy prevention was the patient's responsibility.

Ninety-three percent of the dermatologists was of the opinion he/she adhered to the PPP, see Table 2. Breaking down the PPP to the specific elements for dermatologists, it seemed that only 41 (25%) of the responders adhered to the PPP. Of the 115 responders who agreed on the current PPP, 34 (29.5%) adhered to all elements of the PPP in comparison to those not in agreement on the current PPP or the need of a PPP, 7 responders (15.6%) adhered to the PPP.

Forty-five responders (28%) experienced no problems with adherence to the PPP. Problems on adherence to the PPP were reported by 72% responders. Patient related problems were for instance refusal to use contraceptives due to religion. A concern mentioned by dermatologists was possible under treatment of patients due to refusal of isotretinoin because of the PPP.

Proposals for change or improvement of the PPP by the physicians were given by 75 (47%) of the responders. Proposals ranged from abolition of the PPP to have a more clear information package. Changes proposed more than once were:

- The prevention of pregnancy is only patients' responsibility
- To extend the prescription and control intervals
- To execute the PPP based on judgment of the situation
- To abolish the mandatory pregnancy tests
- To have a patient contract by which it is clear that pregnancy prevention is the responsibility of the patient
- To have a guideline / advice instead of the obligation which can also be used for other drugs with a contraindication for pregnancy

Other proposals were for instance to have GPs or nurses performing the monthly controls, return to the old less restricted PPP, discarding of the informed consent form, exclude the actions for the pharmacist (control of the restricted prescription for 30 days, and delivery within 7 days of the date of prescription).

DISCUSSION

According to the majority of Dutch community pharmacists as well as dermatologists, the main responsibility for the isotretinoin PPP should be with the prescribers. In general, community

pharmacists acknowledge their role of monitoring the isotretinoin PPP, however the programme requirements are not fully adhered to in daily medical practice. Only two out of five pharmacists adhered to all requirements concerning dispensing control, and < 10% reported full compliance with all the elements of the isotretinoin PPP. Adherence of the pharmacists was especially poor in terms of supervision of use of contraception and check of negative pregnancy test results. And adherence did not improve over time even though the PPP has been brought to the attention of pharmacists during this period.

Adherence by the dermatologists seemed less poorly but monthly prescriptions and prescribing of contraceptives was poor. Dermatologists consider themselves more responsible for the execution of the PPP compared to pharmacists. Prescribers are also more alert on pregnancy tests and contraceptive use.

The response rates to the questionnaires are a limitation of the study. It is possible that motivated health care professionals responded. Therefore, our results might present possible a more positive view about the adherence to the PPP. However, response rates of online surveys among pharmacists and physicians might range from 3.1% [14,15] to 75% [16,17], but are mostly between 30-40%. A recent randomised trial among dermatologists shows that dermatologists surveys response rates are often low [18]. A recent publication [19] shows that response rates to web-based questionnaires are becoming comparable to those responding to traditional modes of data collection. The mode of distribution of the questionnaire might not be the reason for this response rate.

Community pharmacists who belong to the UPPER network of Utrecht University and the research group of the Dutch Association of Pharmacists may represent a selected group of pharmacists as they belong to these groups because of their interest in pharmaceutical practice research and/or because they offer internships to pharmacy students. Another limitation of the present study is that responses to questions in the surveys could not be validated. As a consequence, all results reflect pharmacists' or dermatologists' self-reported behaviour. It can therefore not be ruled out that performance of Dutch community pharmacies and dermatologists in general may even be more disappointing. For instance, almost all (93%) of the responding dermatologists thought they adhered to the PPP, but taking into account individual elements of the PPP for prescribers; only a quarter adhered to the PPP as stated in the product information.

Evaluation of implementation of risk minimisation programmes in daily practice is important, because weaknesses might be revealed and could be corrected. Medical literature on this subject is scarce, whereas knowledge on implementation and effectiveness of risk minimisation programmes is essential to achieve full benefits from these programmes. Regulatory authorities may learn from the gaps identified in the present study for future programmes.

No information is available on adherence to the dispensing control element (restriction to 30 day supply and 7 day validity) of the isotretinoin PPP in the Netherlands or in other European countries. Boucher

et al. [20] reported that Canadian pharmacists had given verbal information about teratogenicity and pregnancy prevention to 78% of the women participating in their survey. In addition, pharmacists gave written information other than the package insert to 62% of the women filling their isotretinoin prescription. These results are similar to the results presented in this study. Although our pharmacist surveys did not focus on the physician's role in adherence to the programme, several pharmacists reported that they filled prescriptions that were not limited to 30 days of treatment at physicians' request. In addition, several pharmacists reported that patients presented undated prescriptions. Regretfully, the performance of the PPP by pharmacists did not improve over the years based on the results of both our pharmacists' surveys.

Previous studies showed that the physician's adherence to the isotretinoin PPP should be improved. A retrospective cohort study [21] assessing documentation of use of contraception or recent contraceptive counselling in the US in 2001, the year before institution of the SMART risk management programme, showed that documentation was available in only 62% of isotretinoin prescriptions filled. A more recent US study [22] showed that 9% of qualified prescriptions as part of the SMART programme were issued without a pregnancy test. In addition, a cross-sectional Canadian survey [21] showed that pregnancy testing was poor before and during (every month of) isotretinoin use (44% and 13%, respectively). In this survey, a direct relationship between counselling and recommendations given by physicians and women's use of two forms of birth control was established.

Ultimately, effectiveness of the isotretinoin PPP should be reflected in decreasing numbers of pregnancies exposed to isotretinoin. Evaluation [23] of the SMART programme showed that pregnancy rate for patients participating in the pharmacy compliance survey was comparable to that reported before this programme. Similar result was seen in the evaluation [7] of the even stricter programme iPLEDGE. European data on pregnancies are presented by Autret-Leca *et al* [9]. Reinforcement of the present isotretinoin PPP, however, seems warranted and should involve all stakeholders including marketing authorisation holders (MAHs), national competent authorities, physicians, pharmacists and patients. It should be acknowledged that responsibility for reinforcement of the isotretinoin PPP from the MAHs' point of view is complicated by availability of isotretinoin generics and their widespread use.

Our study suggests that risk management programmes may be supported with provision of educational material to healthcare professionals. Physicians prescribing isotretinoin for the first time and new pharmacists should therefore also be informed about the isotretinoin PPP. Our data suggest that new physicians prescribing isotretinoin may include others than dermatologists alone, and therefore provision of information should not be limited to dermatologists. Enduring awareness of the PPP recommendations and their underlying principles should be maintained among healthcare professionals, and for pharmacies computer alerts seem a helpful tool to achieve this awareness.

One of the interesting results of the present surveys among Dutch community pharmacists and dermatologists is the acknowledgement of their own role in conducting the isotretinoin PPP, and at the same time the fact that pharmacists attribute the main responsibility for the compliance with the

programme to the treating physicians that is confirmed by the dermatologists who acknowledged their responsibility alone or sharing it with the patient. This finding may explain why only a minority of pharmacists (15.4%) reported that they asked for pregnancy test results before every dispensing of isotretinoin to fertile women. Responsibilities are not explicitly laid down in the current isotretinoin PPP and this might be a key issue in the development of new PPPs by the regulatory authorities.

A more proactive approach towards the identification and quantification of safety concerns after marketing has been implemented in the EU in November 2005 by the obligatory submission of an EU Risk Management Plan (EU-RMP). Part of the RMP should evaluate the need for risk minimisation activities and, if considered needed, a description of these activities. Proposals for risk minimisation activities other than pregnancy prevention programmes, e.g. monitoring of laboratory measurements, may also require specific physicians' and pharmacists' achievements and behaviour. The observed non-adherence to the isotretinoin PPP calls for careful evaluation of proposed risk minimisation plans and participation of all stakeholders in the developmental phase of these plans.

According to the majority of Dutch community pharmacists and dermatologists, prescribers are primarily responsible for the isotretinoin PPP. Although pharmacists acknowledge their role in monitoring the isotretinoin PPP, requirements of this programme are adhered to a limited extent in daily pharmaceutical practice. Pharmacists and prescribers could enhance the compliance with the PPP by working together and so complementing each other. Prescribers consider female patients responsible for preventing pregnancy and therefore they should provide the conditions to ensure the highest possible compliance by the patients. These findings are important in view of future programs. Reinforcement of the current isotretinoin PPP is warranted.

ACKNOWLEDGEMENTS

No funding was received for the conduct of the study or preparation of the manuscript.

We would like to thank Prof. P-J Coenraads, dermatologist, Prof. HGM Leufkens, pharmacist and chairman of the Medicines Evaluation Board and Prof. AFAM Schobben, pharmacist and member of the Medicines Evaluation Board for their helpful input. We thank the Dutch Association of Dermatology and Venereology, Dutch Association of Pharmacists and the Utrecht Pharmacy Panel for Education & Research (UPPER) Network for mailing the survey to their members. We would like to thank the participants for completing the questionnaires.

REFERENCES

1. Cheetham TC, Wagner RA, Chiu G, *et al*. A risk management program aimed at preveting fetal exposure to isotretinoin: retrospective cohort study. J Am Acad Dermatol 2006; 55:442-8
2. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol 1992; 26:599-606
3. Sladden MJ, Harman KE. What is the chance of a normal pregnancy in a women where fetus has been exposed to isotretinoin? Arch Dermatol 2007; 143:1187-8
4. Lammer E, Chen D, Hoar R, *et al*. Retinoic Acid Embryopathy. NEJM 1985; 313:837-41
5. Abroms L, Maibach E, Lyon-Daniel K, Feldman SR. What is the best approach to reducing birth defects associated with isotretinoin? Plos Medicine 2006; 11:1978-83
6. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Isotretinoin/human_referral_000086.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024e9a (last accessed on 01 February 2012)
7. Crijns I, Straus S, Luteijn M, *et al*. Implementation of the harmonised EU isotretinoin Pregnancy Prevention Programme: A Questionnaire survey among European Regulatory Agencies. Drug Saf 2012; 35:27-32
8. Shin J, Cheetham T, Wong L, *et al*. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health system. J Am Acad Dermatol 2011; 65:1117-25
9. Autret-Leca E, Kreft-Jais C, Elefant E, *et al*. Isotretinoin exposure during pregnancy – Assessment of spontaneous reports in France. Drug Saf 2010; 33:659-65
10. Teichert M, Visser L, Dufour M, *et al*. Isotretinoin use and compliance with the Dutch Pregnancy Prevention Programme A retrospective cohort study in females of reproductive age using pharmacy dispensing data. Drug Saf 2010; 33:315-26
11. Crijns H, van Rein N, Gispen-de Wied C, *et al*. Prescriptive Contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study. Pharmacoepidemiol Drug Saf 2012 doi: 10.1002/pds.3200
12. Arriegas M, Pégo A, Lemos M, Clérigo I. Isotretinoin – PPP compliance. Drug Saf 2009; 10:984
13. Jeanmougin M, Beaulieu P, Doutre M, Jaramillo C. Aide au bon usage de l'isotrétinoïn en pratique libérale: observatoire prospectif de 1263 patients acnéiques. Ann Dermatol Venereol 2009; 136:54-61
14. Asbell PA, Spiegel S. Ophthalmologist perceptions regarding treatment of moderate to severe dry eye: Results of a physician survey. Trans Am Ophthalmol Soc 2009; 107:205-13
15. Handler SM, Shierts BH, Perera S, *et al*. Frequency of laboratory monitoring of chronic medications administered to nursing facility residents: results of a national Internet-based study. Consult Pharm 2008; 23:387-95
16. Metcalfe PD, Elyas R. Foreskin management – Survey of Canadian pediatric urologists. Can Fam Physician 2010; 56:e290-5
17. Wilbur K. Resident physician and hospital pharmacist familiarity with patient discharge medication costs. Pharm World Sci 2009; 31:195-201
18. Wan J, Abuabara K, Shin DB, Troxel AB, Bebo BF Jr, Gelfand JM. Dermatologist response rates

to a mailed questionnaire: A randomised trial of monetary incentives. J Am Acad Dermatol 2012; 66:e18-e20

19. Van Gelder M, Bretveld R, Roeleveld N. Web-based Questionnaires: The Future in Epidemiology? Am J Epidemiol 2010; 172:1292–8
20. Boucher N, Beaulac-Baillargeon. Pregnancy Prevention among women taking isotretinoin: failure to comply with the recommendations. Can Fam Physician 2006; 52:339-42
21. Schwarz EB, Postlethwaite DA, Hung YY, Armstrong MA. Documentation of contraception and pregnancy when prescribing potentially teratogenic medications for reproductive-age women. Ann Intern Med 2007; 147:370-6
22. Bérard A, Azoulay L, Koren G, *et al*. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Clin Pharmacol 2007; 63:196-205
23. Brinker A, Kornegay C, Nourjah P. Trends in adherence to a revised risk management program designed to decrease or eliminate isotretinoin-exposed pregnancies. Arch Dermatol 2005; 141:563-9

- 67% of the patients heard about the isotretinoin PPP from their treating physician.
- 6% of the patients used isotretinoin for mild acne instead of moderate to severe acne.
- 61% of the patients had a pregnancy test before starting isotretinoin treatment. 33% performs pregnancy tests on a monthly basis.
- 11% of the pharmacists did ask for pregnancy test results.
- 61% of the patients receives prescriptions covering one month treatment and 33% received prescriptions for three months.
- 72% of responding patients uses contraceptive measures, the remaining patients were not sexually active. 17% did not use contraceptive measures with every sexual contact.
- 50% of the patients considers the PPP a mutual responsibility of prescriber and patient.

Results patient survey (*n*=18)

Chapter 4.2

Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study

Hubertina JMJ Crijns[1,2] , Nienke van Rein[1], Christine C Gispen-de Wied[2], Sabine M Straus[2,3], Lolkje TW de Jong-van den Berg[1]

1. University of Groningen, Department of PharmacoEpidemiology & PharmacoEconomics, Groningen, the Netherlands,
2. Medicines Evaluation Board, The Hague, the Netherlands
3. Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands.

Pharmacoepidemiol and Drug Saf 2012 Jan 6; DOI:10.1002/pds.3200

ABSTRACT

Purpose

To assess the compliance with the isotretinoin Pregnancy Prevention Programme (PPP) by evaluating the use of prescribed contraceptives among isotretinoin users. The PPP contains a requirement for the use of contraceptive methods for women of childbearing potential.

Methods

A drug utilisation study was performed using data from a drug prescription database (containing Dutch community pharmacy data) covering a population of 500,000 patients. Contraceptive use in female isotretinoin users and in a reference group of female non-isotretinoin users (aged 15-49 years) was compared using data from 1999 until 2006 in two year periods. Descriptive statistics were used.

Results

Of the female isotretinoin users (*n*=651), 52-54% filled prescriptions on contraceptives in strict accordance to the PPP, used before, during and after discontinuation of isotretinoin, compared to 39-46% in the reference group. A more liberal approach of a minimum of one prescription for a contraceptive method showed 61-64% use of contraceptives among isotretinoin users. Similar patterns were seen when data were broken down in age groups. Furthermore, a higher proportion of female patients using isotretinoin prescribed by general practioners used prescribed contraceptives compared to those receiving isotretinoin by specialists.

Conclusion

Compliance with the contraceptive use according to a PPP for a teratogenic drug such as isotretinoin is 52-64% which is lower than anticipated. Reasons for the low compliance will need to be clarified before further measures can be taken.

INTRODUCTION

Isotretinoin is a vitamin A derivative used for the treatment of severe acne which has failed to respond to conventional acne therapy.

Dutch studies on the prevalence of acne in general practice showed a range between 30-90%, depending on the definition [1]. A study in the UK [2] and a study in Germany [3] show a prevalence of clinical acne in women of 23% and 24%, respectively. Only 10% of both male and female acne patients experience severe acne, defined as having at least 20 papules and/or pustules had used systemic treatment and <1% of all acne patients ever used isotretinoin [4].

Because vitamin A derivatives are highly teratogenic in humans, a strict pregnancy prevention programme (PPP) is in place.

Isotretinoin was authorised in the USA in 1982 and in Europe in 1983. In 1983 [5], the first cases of congenital anomalies appeared despite a contra-indication for pregnancy because of the teratogenic risk of vitamin A derivatives. Therefore, in 1983, the product information was revised by the Marketing Authorisation Holder (MAH), Roche. Additional steps were taken such as placing a text about teratogenicity in the product information and letters were sent to prescribers and pharmacists with additional information on the warnings. Worldwide, a PPP was implemented by Roche in 1988. In the USA, this PPP has been amended twice thereafter, in 2001 (System to Manage Accutane Related Teratogenicity [SMART]) and in 2006 (iPLEDGE; a more stringent programme in which prescribers, patients, pharmacists and wholesalers are registered in an online database) [6]. In 2003, in Europe, due to the entrance of generic products containing isotretinoin on the market, a regulatory referral was performed to harmonise the indication for isotretinoin as well as the PPP [7]. The prevalence of congenital anomalies with isotretinoin is about 26% in live births [8]. The aim of these PPPs is to avoid pregnancies before, during the use and one month after discontinuation of isotretinoin because of the high risk of congenital anomalies.

A PPP is a risk minimisation measure as defined in the guideline [9] on risk management plans. In this case, the risk of exposure to isotretinoin during pregnancy and indirectly a risk on congenital anomalies should be avoided. Elements of the PPP of isotretinoin are presented in Box 1. The use of contraceptives by female isotretinoin users might provide an indication of the effect of the PPP.

During recent years cases of *in utero* exposure of isotretinoin have been identified despite the PPP [10,11]. For regulatory authorities, it is important to gain insight in the compliance with the PPP, which is intended to gain 100% avoidance of pregnancies. The use of contraception by female isotretinoin users could be an indication of compliance with the PPP, which can be assessed and quantified in contrast to some of the other elements of the PPP. We performed a drug utilisation study with the data of a Dutch community pharmacies database (IADB.nl) to evaluate the use of contraceptives among female isotretinoin users as main outcome. To measure whether the PPP had effect, the use

of contraceptives in female isotretinoin users was compared with contraceptive use in the general population in the same age group. In addition we evaluated different aspects (e.g. compliance in urban vs. rural areas, innovator product vs. generic formulations of isotretinoin, first prescriber and isotretinoin preceded by prescribed conventional therapy vs. no preceding conventional therapy) that might influence the use of contraceptives and thereby indirectly the adherence to the PPP.

MATERIALS AND METHODS

Database

Data of Dutch community pharmacies are obtained from IADB.nl [12]: a database which contains prescriptions of a population of approximately 500,000 individuals from the Netherlands. The data in the database consist of among others personal characteristics (an anonymous identifier, gender and date of birth) and drug information as Anatomical Therapeutic Chemical (ATC) code [13] of the World Health Organisation, the dispensing date, the theoretical end date and the prescriber [12,14]. Dutch patients commonly register with one pharmacy and mainly obtain their prescription medication from this pharmacy, so medication histories of patients can be considered nearly complete [15].

Study population

The study covered the period of 1999 to 2006. Both males and females aged 15-49 years using isotretinoin were selected (*n*=1825).

Isotretinoin users to be included in the study were determined by the first prescription of isotretinoin in the database, which has to be at least 180 days after the date the patient first appeared in the database.

The prevalence rates of male and female isotretinoin users were compared in general and specifically for first-time prescribers of isotretinoin, for example specialists or general practioners (GPs).

Reference population

The population aged 15-49 years in the area covered by the community pharmacies participating in the data base during the period 1999-2006.

Isotretinoin use among female users

We selected in this dataset female patients aged 15-49 years who had received any isotretinoin prescription during the study period. Two-year prevalence of female isotretinoin users was calculated. The ATC code for systemic isotretinoin, D10BA01, was used. The two-year prevalence was defined as the number of female isotretinoin users that received at least one prescription in a two-year period divided by the population in that age group.

Contraceptive use among female isotretinoin users

We selected in this dataset female patients aged 15-49 years who had received any isotretinoin prescription during the study period. In this group of isotretinoin users (*n*=651), contraceptive use

was calculated and compared with the use of contraceptives in the population of female non-users of isotretinoin between 15 and 49 years of age (reference group).

Prescriptive contraceptive methods have been defined as all forms of intrauterine devices (IUDs), hormonal implants, oral contraceptives (including cyproteron acetate / ethinyl-estradiol [CPA/EE]) and depot medroxyprogesterone acetate The period of use for these contraceptions was considered to be one year for the oral and depot contraceptives, three years for the hormonal implants and five years for the IUDs.

The use of contraceptive methods among isotretinoin users was calculated by two methods: 1) a liberal method: the number of women who had at least one prescription of a contraceptive in the period described earlier for the different contraceptive methods as the isotretinoin prescription divided by the total number of isotretinoin users and 2) a strict method: in which the period of contraceptive use has been defined as 30 days before isotretinoin was used, the duration of its use, and 30 days after the use of isotretinoin ended.

The use of contraceptives in the reference group was calculated as the number of women (isotretinoin non-users) in the age group of 15 through 49 years with at least one contraceptive prescription divided by the female population (15-49 years) of the covered area.

Other variables

Among the female isotretinoin users, we also compared the compliance with the PPP related with other variables as area (rural vs. urban), type of isotretinoin formulation (innovator product vs. generic products), first prescriber of isotretinoin (specialist vs. GP), preceding use of conventional anti-acne medication and type of contraceptive (CPA/EE vs. others).

- Urban areas are defined as cities with at least 100,000 citizens and rural areas were all other areas. There have been suggestions of better adherence differences on drug use in rural areas compared to urban areas [16,17], which triggered the question on the compliance of contraceptives and isotretinoin in these areas.
- The performance with the innovator product Roaccutane® was compared with the performance using generic products of isotretinoin. The innovator and the generic products were determined by the trading product code (hpk in Dutch) number; an identification number for every product that is on the market in the Netherlands, that can distinguish different brands [18]. The MAH of the innovator Roaccutane® with long-time of experience with a PPP for isotretinoin in contrast with the MAH of generic products of isotretinoin but despite the harmonised European PPP for isotretinoin it was considered useful to compare compliance with the contraceptive use as part of the PPP among these products.
- Contraceptives prescribed for female isotretinoin users with first prescriber of isotretinoin, specialist or GP, was analysed. Isotretinoin may be prescribed by physicians known with the product. A study performed in France [19] showed that GPs did perform less than dermatologists.

- Conventional anti-acne medication was defined as the first-line medication for treatment of acne according to standards for dermatologists and for Dutch GPs [20]. Contraceptive use in female isotretinoin users with prescribed conventional anti-acne medication before isotretinoin use was compared with those without preceding prescriptions of conventional anti-acne medication. Prescription of conventional medication before isotretinoin is part of a guideline [1], considering the PPP as a guideline, therefore the theory that in case a prescriber did not follow one guideline he or she would be also not follow the PPP for isotretinoin.
- Proportion of users of the combination preparation of CPA/EE in the female isotretinoin user group was compared with the proportion of CPA/EE in the reference group. CPA/EE is not licensed as a contraceptive [21]; it is licensed for the treatment of acne in female patients but also has contraceptive properties and therefore used as such in daily practice. From literature [22], it is known that women with acne will use more often CPA/EE as a 'contraceptive', despite that it is not licensed for this indication.

Statistics

Descriptive statistics were used, calculation of proportions in percentage with 95% Confidence Intervals (95%CI), if applicable. Based on these confidence intervals, statistical significant differences with the reference population could be determined.

RESULTS

During 1999-2006, we identified 1825 isotretinoin users in the IADB.nl database between 15 and 49 years of age. The group of isotretinoin users consisted of 64% male users (*n*=1171) and 36% female users (*n*=651).

The proportion female isotretinoin users versus male patients was higher with the specialist compared to the GP, 64% and 40%, respectively.

The prevalence of contraceptive use among the female isotretinoin users in both analyses the more strict definition (52%-54%) as well as with the more liberal (61%-64%) was compared with contraceptive use in the female general population (39%-46%) showing a significant higher proportion of contraceptive use in both isotretinoin groups (see Table 1 and Figure 1).

Rural areas have a better compliance with contraceptive use compared to the urban area (see Table 1). In the periods 2003-2004 and 2005-2006, there is even an increase in compliance in the rural areas compared with the urban areas. Comparison with a reference group of contraception users, the urban female isotretinoin users have a lower proportion of contraception use from 2003 onwards (see Table 1). Rural female isotretinoin users with contraception have a better compliance than a reference group of rural contraception users from 2003 onwards (see Table 1).

Use of contraceptives with the innovator product versus the generic products containing isotretinoin was compared. The generic isotretinoin formulations came on the market from 2003 onwards; only the last two-year periods have data for comparison and show a statistically better performance with the innovator product in the period 2005-2006 (see Table 1).

The compliance of contraceptive use with the origin of first prescriptions of isotretinoin was compared. The proportion of contraceptive users in the female population was significantly lower in the specialist group compared to the GP group, 63% versus 71%, respectively.

The use of prescribed contraceptives in female isotretinoin users who had prescriptive conventional treatment of acne preceding use of isotretinoin was compared with isotretinoin use without preceding prescribed conventional acne therapy. The proportion of prescribed contraceptives in the group of female isotretinoin users with preceding conventional anti-acne treatment was 66% (61-71 [95%CI], *n*=236) compared to 41% (32-50 [95%CI], *n*=46) in the group without preceding conventional anti-acne medication, which is statistically significantly higher. The compliance of specialists and

GPs in the group of female isotretinoin users with preceding prescriptive conventional anti-acne medication and contraception was similar, 52% and 48%, respectively. However, in the group of female isotretinoin users without preceding prescriptive conventional anti-acne medication and contraception the compliance of specialists was higher than GPs, 63% and 37%, respectively.

Table 1. Data from the female population aged 15-49 years in the database for different variables.

	1999-2000	**2001-2002**	**2003-2004**	**2005-2006**
	n (%, [95%CI])	**n (%, [95%CI])**	**n (%, [95%CI])**	**n (%, [95%CI])**
Isotretinoin and contraceptives (PPP)#	121 (54, [47-61])*	108 (54, [47-61])*	103 (54, [47-61])*	83 (52, [44-60])*
Isotretinoin and contraceptives$	142 (64, [57-70])*	124 (62, [56-69])*	116 (61, [54-67])*	98 (62, [54-69])*
Reference group and contraceptives	80778 (45.7 [45.5-45.9]	80412 (44.6 [44.4-44.8]	80814 (43.0 [42.8-43.2]	79944 (39.1 [38.9-39.3]
Age	**n (%)**	**n (%)**	**n (%)**	**n (%)**
15-24				
Isotretinoin and contraceptives (PPP)	47 (62)	48 (57)	44 (55)	36 (50)
Reference group and contraceptives	28846 (54)	28646 (56)	28968 (56)	28139 (51)
25-34				
Isotretinoin and contraceptives (PPP)	51 (61)	44 (61)	38 (53)	29 (63)
Reference group and contraceptives	30894 (54)	29353 (56)	28607 (55)	27496 (51)
35-49				
Isotretinoin and contraceptives (PPP)	23 (37)	16 (37)	21 (55)*	18 (44)*
Reference group and contraceptives	20392 (25)	21681 (26)	22372 (25)	23320 (23)
Innovator versus generic isotretinoin				
Innovator with contraceptives	121 (54)	108 (54)	63 (56)	48 (66)**
Generic with contraceptives	-	-	57 (55)	44 (45)
Urban areas versus rural areas				
Urban				
Isotretinoin users and contraceptives	78 (53)	66 (54)	58 (49)	41 (43)
Reference group and contraceptives	46660 (56)	44715 (55)	43544 (54)	41401 (52)
Rural				
Isotretinoin users and contraceptives	43 (56)	42 (55)	45 (63)	42 (67)¥
Reference group and contraceptives	33291 (57)	33480 (57)	33279 (56)	32306 (53)

CI, confidence interval; PPP, Pregnancy Prevention Programme.
Strict contraceptive use in accordance with PPP
$ Liberal contraceptive use
* Statistical significant higher compared to the reference group
** Statistical significant higher compared to comparator group generic formulations
¥ Statistical significant higher compared to the urban isotretinoin users group and to the rural reference group

The proportion of CPA/EE of the contraceptives used in the isotretinoin user group is 59.9%. In the reference group the use of CPA/EE is below 9.6% of the contraceptive use.

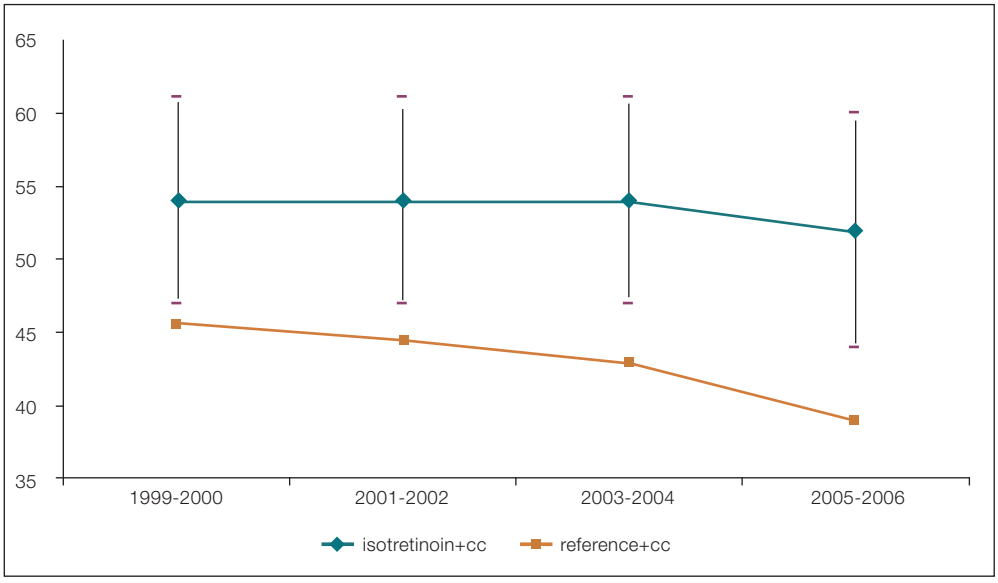

Figure 1. Distribution (%) of prescribed contraceptives in isotretinoin users according to the strict definition of the PPP and controls.

DISCUSSION

In this study a significantly higher use of prescribed contraceptives was found among female isotretinoin users using contraceptives in accordance with the PPP (52-54%) as well as with liberal use of a minimum of one prescription of a contraceptive method (61-64%) compared with the use of prescribed contraceptives in the female general population, reference group (39-46%). Compliance with contraceptive use among female isotretinoin users was also better in rural versus urban areas as well as with preceding therapy of conventional anti-acne treatment compared with no preceding therapy. Furthermore, female patients using isotretinoin prescribed by general practioners had a better performance compared to those receiving isotretinoin by specialists.

Limitation of the study is the lack of information on barrier methods, such as condom use, and on sterilisation of the female isotretinoin users. Therefore, there will be underrating of the contraceptive methods for both isotretinoin users and the reference group. For example, for 2008, Statistics Netherlands [23] shows that a proportion of 3% of all Dutch women are sterilised and that 9% used a condom for contraception. Further limitation might be the lack of explanations for the lower compliance with contraceptive use among female urban isotretinoin users and contraception even lower than the reference group.

The strength of this study is the comparison of contraceptive use among isotretinoin users compared to contraceptive use among non-isotretinoin users. In addition, several aspects related to prescribing isotretinoin and contraceptives are studied, for instance, compliance related to first prescribers and preceding conventional anti-acne medication.

The PPP for isotretinoin contains among others a requirement of the use of contraceptive measurements for women of childbearing age. Preferable two methods should be used, one of which should be a barrier method. Because of this condition for prescribing isotretinoin to women of childbearing age, the use of prescribed contraceptives in accordance with the PPP would be ideally expected to have an almost 100% coverage in addition to the barrier methods. In the end, it seems that the PPP has received some attention because of the 10-20% higher usage of prescribed contraceptives in the female isotretinoin users group compared with the female general population.

The proportion of women using prescribed contraceptive methods in the Dutch population by Statistics Netherlands [23] was 45% in 1998 and 46% in 2003. According to these data, the use of prescribed contraceptives reference group is comparable to use in the general Dutch population justifying female non-users of isotretinoin in the IADB.nl database as reference.

A recent study by Teichert *et al*. [24] showed at the stringent analysis of contraceptive use in female isotretinoin user population a comparable proportion of contraception use with that in our analysis. The study by Teichert *et al*. and our study are complementary and provide a good insight in the compliance of contraception use among female isotretinoin users in the Netherlands.

Despite the fact that CPA/EE should not be used solely as a contraceptive, women with acne will use this combination preparation of CPA and EE as conventional anti-acne medication as well as contraceptive and will continue using it as contraceptive during use of isotretinoin despite the recommendation to stop after treatment of 3 to 4 months. If CPA/EE would be excluded as a contraceptive, the contraception compliance in female isotretinoin users would be very low. Regulatory authorities could use this as an opportunity to inform prescribers and pharmacists on this phenomenon and the substantial off-label use of CPA/EE as contraceptive.

Prescribers not following the guidelines for treatment including the one on acne might also tend to neglect the PPP of isotretinoin. This might be an explanation for the smaller proportion of contraceptive use among isotretinoin users without preceding conventional anti-acne medication. Although it would be expected from the overall better compliance of GPs regarding contraceptive use in female isotretinoin users, the compliance of GPs in the subgroup of female isotretinoin users without preceding conventional anti-acne treatment was much lower compared to specialists.

Prescribed oral contraceptives have a pearl-index of 1-2% and therefore do not guarantee 100% pregnancy prevention. The pearl-index is used for contraceptive methods and is a rate determined by the number of unintentional pregnancies related to 100 women years. Moreover, during the first

week after the pill-free period missing pills seems to occur [17] which can result in an unplanned pregnancy. In addition it was shown that even women with fairly good contraceptive compliance sometimes experienced unplanned pregnancies [25]. These data are a reason to use a second contraceptive method preferably a barrier method.

The data suggest that education of prescribers and pharmacists involved in the PPP might need specific attention and focus to enhance the performance and adherence, and also reminders that the PPP is mandatory might be helpful. Pharmacists, among others, with the task of controlling prescriptions might feel specifically responsible for the requirement of the restricted prescription of isotretinoin for female users of 30 days and the fact that there is a time limit on the prescription of 7 days. Together with prescribers, they might take a role in creating awareness of these requirements.

In the database, there are more females receiving prescribed medication than males are. In contrast, isotretinoin which has been more prescribed for male patients (0.57%) than female patients. This could be due to higher prevalence of severe acne in man compared with women or because of the teratogenicity that isotretinoin will be less prescribed for women (0.27%).

Compliance with use of contraceptive methods as part of risk minimisation measures such as a PPP for teratogenic drugs is lower than would be anticipated. Adherence to the PPP is a joint responsibility of regulatory authorities (to develop a good programme and create awareness), prescribers (to inform patients and perform specific investigations), pharmacists (to monitor adherence) and ultimately patients to adhere to specific requirements. Reasons for this low compliance should be clarified first in order to implement improvements or before further measures can be taken.

REFERENCES

1. Standard of Dutch College of General Practioners: Acne
2. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. Br Med J 1979;1:1109-1110
3. Schäfer T, Nienhaus A, Vieluf D, *et al*. Epidemiology of acne in the general population: the risk of smoking. Br J Dermatol 2001;145:100-104
4. Nijsten T, Rombouts S, Lambert J. Acne is prevalent but use of its treatments is infrequent among adolescents from the general population. JEADV 2007;21:163-168.
5. Rosa F. Teratogenicity of isotretinoin. Lancet 1983; 322:513
6. Abroms L, Maibach E, Lyon-Daniel K, Feldman SR. What is the best approach to reducing birth defects associated with isotretinoin? Plos Med 2006 Nov;3:1978-83.
7. www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Isotretinoin_29/WC500010882.pdf [assessed 17 March 2011]
8. Lammer E, Chen D, Hoar R, *et al*. Retinoic Acid Embryopathy. NEJM 1985 Oct; 313:837-41
9. Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Eudralex, version September 2008.
10. Autret-Leca E, Kreft-Jais C, Elefant E, *et al*. Isotretinoin exposure during pregnancy – Assessment of spontaneous reports in France. Drug Saf 2010; 33:659-665.
11. Shin J, Cheetham T, Wong L, *et al*. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. J Am Acad Dermatol DOI:10.1016/j.jaad.2010.09.017.
12. www.iadb.nl [assessed 17 March 2011]
13. www.whocc.no/atc [assessed 15 August 2010]
14. Vegter S, Kölling P, Töben M, *et al*. Replacing hormone therapy-is the decline in prescribing sustained, and are nonhormonal drugs substituted? Menopause 2009; 16:329-35.
15. Tobi H, van den Berg PB, de Jong-van den Berg LTW (2000) The interaction database: synergy of science and practice in pharmacy. In: Brause RW, Hanisch E, (eds) Medical data analysis. Springer, Berlin Heidelberg New York, pp 206–211.
16. Egede LE, Gebregziabher M, Hunt KJ, Axon RN, Echols C, Gilbert GE, Mauldin PD. Regional, geographic and ethnic differences in medication adherence among adults with Type 2 Diabetes. Ann Pharmacother 2011;45:169-178
17. Aubeny E, Buhler M, Colau J-C *et al*. Oral contraception: patterns of non-compliance. The Coraliance study. Eur J Contracept Reprod Health Care. 2002;7:155-161
18. www.z-index.nl [assessed 15 August 2010]
19. Autret-Leca E, Jonville-Béra A-P, Szafir D, *et al* Roaccutane chez la femme en âge de procréer : étude de l'impact du renforcement des recommandations de prescription. Ann Dermatol Venereol 2000 ;127 :808-813.
20. Kertzman MGM, Smeets JGE, Boukes FS, Goudswaard AN. Samenvatting van de standaard 'Acne' (tweede herziening) van het Nederlands Huisartsen Genootschap. Ned Tijdschr Geneeskd 2008;152:1271-1275
21. Summary of Product Characteristics of Diane-35®. http://db.cbg-meb.nl/IB-teksten/h11903.pdf

[assessed 6 September 2011]
22. Seaman HE, de Vries CS, Farmer RD. Differences in the use of combined oral contraceptives amongst women with and without acne. Hum Reprod 2003;18:515-521
23. www.statline.cbs.nl [assessed 25 June 2010]
24. Teichert M, Visser L, Dufour M, *et al*. Isotretinoin use and compliance with the Dutch Pregnancy Prevention Programme A retrospective cohort study in females of reproductive age using pharmacy dispensing data. Drug Saf 2010;33:315-326.
25. Sundby J, Swanemyr J, Mæhre T. Avoiding unwanted pregnancy - the role of communication, information and knowledge in the use of contraception among young Norwegian women. Patient Education and counseling 1999;38:11-19.

Box 1 Elements of the isotretinoin Pregnancy prevention programme

- Contraindication pregnancy
- Information for patient (both male and female) regarding teratogenicity
- Educational material for patient (only female)
- Contraception brochure
- Informed consent form for women of childbearing potential to sign
- Pregnancy tests before, during and after treatment of isotretinoin
- Supply restrictions of isotretinoin for women of childbearing potential to 30 days per prescription and a prescription has a validity of 7 days
- At least one method of contraception, preferably two method of which one method is a barrier method
- Isotretinoin should only be used by the person for which it is prescribed
- Patients using isotretinoin should not donate blood up to and including to at least one month after discontinuation

- 67% of the patients heard about the isotretinoin PPP from their treating physician.
- 6% of the patients used isotretinoin for mild acne instead of moderate to severe acne.
- 61% of the patients had a pregnancy test before starting isotretinoin treatment. 33% performs pregnancy tests on a monthly basis.
- 11% of the pharmacists did ask for pregnancy test results.
- 61% of the patients receives prescriptions covering one month treatment and 33% received prescriptions for three months.
- 72% of responding patients uses contraceptive measures, the remaining patients were not sexually active. 17% did not use contraceptive measures with every sexual contact.
- 50% of the patients considers the PPP a mutual responsibility of prescriber and patient.

Results patient survey (*n*=18)

Chapter 4.3

Pregnancy exposure to systemic isotretinoin in the Netherlands
A descriptive study

Ineke Crijns[1,2], Loes de Vries[3], Sabine Straus[2,4], Lolkje de Jong-van den Berg[1], Kees van Grootheest[3,5]

1) University of Groningen, Department of PharmacoEpidemiology & PharmacoEconomics, Groningen, the Netherlands
2) Medicines Evaluation Board, Pharmacovigilance department, Utrecht, the Netherlands
3) Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands
4) Erasmus Medical Center, Department of Medical Informatics, Rotterdam, the Netherlands
5) University of Groningen, Department of Pharmacotherapy and Pharmaceutical Care, Groningen, the Netherlands

Submitted

ABSTRACT

Background

In the European Union (EU), studies investigating isotretinoin pregnancy exposure were performed in several countries and throughout the EU indicating that pregnancies still occur despite the implementation of a Pregnancy Prevention Programme (PPP). Therefore, information was collected concerning the compliance with the PPP in isotretinoin exposed pregnancies retrospectively and on different aspects of failure of the PPP.

Methods

The seventeen health care professionals (HCPs) who had contacted the Dutch Teratology Information Service (TIS) during 2007-2011 about isotretinoin exposure during pregnancy were selected. A questionnaire was sent to these HCPs for additional information on the exposed pregnancies by mail.

Results

Overall response rate was 88.2% (15/17), but the response rate of completed questionnaires (*n*=9), was 52.9% (9/17). Mean age of the exposed women was 26.6 years (range 22-35 years). Most of the women discontinued isotretinoin at gestational week 4-6. Contraceptive measures were not adequately or not at all performed. Known outcomes were spontaneous abortion (4x), terminated pregnancy (2x), a live born baby (2x) and one pregnancy is ongoing. One live born infant had congenital anomalies and ultrasound examination of the ongoing pregnancy showed a possible anomaly. Education of the patients about the risks of isotretinoin exposure pregnancy scored 'excellent' by the contacted HCPs.

Conclusion

The failure of the PPP regards not the education of patients on the consequences of isotretinoin exposed pregnancy but the poor compliance with or the absence of contraceptive use. This might implicate that the focus to enhance the performance of the PPP should be on compliance with contraceptives.

INTRODUCTION

The first reports on congenital anomalies due to intra-uterine exposure of isotretinoin appeared in 1983 in the US [1]. The isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system anomalies2. The critical period for isotretinoin exposure during pregnancy appears to start 2 weeks following conception and may cause a 40% rate of spontaneous abortion and shows an approximately 25% risk of the embryopathy [2,3]. Developmental delays and other Central Nervous System (CNS) effects may occur at high frequencies [4].

Isotretinoin is a vitamin A derivative and is authorised in Europe in 1983 for the treatment of severe acne. Because of its high risk of teratogenicity in humans a pregnancy prevention programme (PPP) has been established in 1988. In 2003, following a regulatory procedure this programme was strengthened and harmonised for all systemic isotretinoin formulations in the European Union (EU) [5].

In the EU, studies investigating exposure to isotretinoin during pregnancy were performed in France [6], Italy [7], Germany [8], and throughout the EU [5]. These studies demonstrate that despite an implemented PPP pregnancies still occur. Most frequently reported pregnancy outcomes were either spontaneous abortion or elective termination of the pregnancy. For example, in the German study, there were 69 elective terminations and five spontaneous abortions in 91 pregnancies with known outcome. These pregnancies were exposed to isotretinoin one month before and/or during pregnancy. In general, decisions on elective terminations were taken for fear of the risks of isotretinoin exposure during pregnancy [8]. Drug utilisation studies on contraceptive use by women of childbearing potential while using isotretinoin indicate that 50-60% used prescriptive contraception [9,10].

Teratology information service (TIS) is a centre of expertise on the possible effects of drug use and other exposures on human reproduction. The Dutch TIS is currently part of the Netherlands Pharmacovigilance Centre Lareb and member of the European Network of Teratology Information Services (ENTIS) (www.entis-org.com). The expertise of TIS is shared with health care professionals (HCPs) (www.lareb.nl). In addition, TIS as an information centre has a telephone service for consultation. Information provided concerns general or individual information on drug exposure during the preconception period, pregnancy, lactation or spermatogenesis. However, the focus of TIS is communication about individual risk estimation. In case of exposures to drugs with increased risk of congenital anomalies or when limited information on pregnancy outcome is available follow up will take place. In this study prospective cases of isotretinoin exposure during pregnancy were investigated by performing a survey among the health care professionals who had contacted TIS regarding these cases.

The aim of this study was to collect information concerning the compliance with the PPP in these isotretinoin exposed pregnancies retrospectively and collect information on the different aspects of failure of the PPP.

MATERIALS AND METHODS

Cases in which exposure to isotretinoin occurred during pregnancy were identified. Health care professionals (HCPs) who contacted the Dutch TIS during a five year period, 1 January 2007 through 31 December 2011, for information on isotretinoin exposure during pregnancy were sent a questionnaire by mail for additional information.

The structured questionnaire contained a combination of 10 closed and open questions, see box 1. The cover letter contained the already available information at TIS on this case, obtained during the initial telephone contact and/or the standard follow-up procedure. The first question concerned verification of the available information at TIS on the case and if information was correct, the initial information was used in the analyses.

Descriptive statistics were used.

Box 1: Questionnaire sent to health care professionals who contacted the Dutch teratology information service for information on isotretinoin during pregnancy, abbreviated.

1. The cover letter contains the available data, are these correct?
2. Initials (of the patient): Year of birth: 19…….
3. Treatment period with isotretinoin:
   Date of conception:
   Date last menstrual period:
4. Used contraceptive method(s)?
5. Pregnancy outcome?
6. Were congenital anomalies present?
7. Did the patient use concomitant medication?
8. Who prescribed isotretinoin to this patient?
9. Please provide you opinion on the education of the possible consequences of an isotretinoin exposed pregnancy on a scale of 1-10 (1= very bad / 10 = nothing to comment).
10. Were there additional patients with isotretinoin exposed pregnancies in you practice?

RESULTS

During the five year period of 2007-2011, the Dutch TIS received questions about 17 prospective cases of isotretinoin exposure during pregnancy. HCPs contacting TIS about these cases were gynaecologists or gynaecologists in training (*n*=13), general practitioners (*n*=2), one midwife and one abortion physician.

Fifteen questionnaires (88.2%) were returned either with a completed questionnaire (*n*=9 [52.9%]) or with the questionnaire still open (*n*=6) because of loss to follow up. Results of the nine completed

questionnaires including available data on these cases are presented in Table 1. Data available of the remaining eight cases is presented in Table 2.

The mean age of the exposed women was 26.6 years (range 22-35 years). Isotretinoin exposure occurred until gestational week 4 in 10 cases, until gestational week 6 in 5 cases and there were single cases in which exposure took place from week 9-12.5 or the information was missing.

In eight cases, the pregnancy outcome was unknown. In four cases, the pregnancy outcome consisted of a spontaneous abortion and in two cases pregnancy was terminated. Two pregnancies resulted in live born babies and one pregnancy is still ongoing.

Six out of the nine completed questionnaires (66.7%) responded that the information available from the telephone interviews was correct (Q1).

Information on contraceptive methods was not known in two cases. Two responders explicitly mentioned that the patient did not use a contraceptive method (Q4).

Congenital anomalies were reported in one live born infant, consisting of anomalies of external ears, agenesis of the right auditory canal and severe hearing loss on both sides, but no neurologic pathology was diagnosed at 4 months of age. These anomalies resemble anomalies form the retinoid embryopathy [2]. Ultrasound examination of the foetus of the ongoing pregnancy showed a malformation of the vermis of cerebellum (Q6).

The question regarding the education on the risk of isotretinoin exposure during pregnancy (Q9) was scored seven times of which six times the rate was '8-10' and once a '1'. In case explanatory opinions on the education by the participating HCPs were provided, it was mentioned that the patients were well informed. The patients were informed, because monthly pregnancy tests were done and the patient discontinued at the moment the test was positive, or the patient had reported that she had signed an informed consent form or these HCPs were aware of communication on the use of isotretinoin and pregnancy prevention with their patient by the isotretinoin prescriber.

Table 1 Data available with responding health care professional of patients with isotretinoin exposure during pregnancy

Year	Age years	Period of exposure during pregnancy	Dose	Prescriber	Contraception Yes/no	Contraceptive method	Concomitant medication / recreational drugs	Ultrasound examination	Pregnancy outcome
2008	27	Until week 2, week 3-5.5	30 mg daily, 40 mg daily		'yes'	Diane-35*, forgotten twice			Full term Congenital anomalies
2008	29	Until 4 weeks		Dermatologist		Possibly condoms		Twin pregnancy	Spontaneous abortion at 14th week
2008	35	Week 6	Single dose of 20 mg	Dermatologist	No		None		Full term, no congenital anomalies
2009	27	Until 2.5 weeks			'yes'	Diane-35, stopped	None	Missed abortion	
2010	25	2-5 weeks	40 mg daily	Dermatologist	Yes	Oral anti-contraceptive	None		Spontaneous abortion at 9 weeks
2010	25	Until 4 weeks	10 mg daily	Dermatologist	Yes	Condoms	None		Terminated pregnancy
2010	30	At 4 weeks, for 3 days	40 mg daily		'yes'	Diane-35, stopped	venlafaxine and methylphenidate	Empty amniotic cavity at 5th week	Terminated pregnancy
2010	22	Until 2 or 6 weeks**		Dermatologist			dapsone	Normal at 20 weeks	
2011	24	Until 6 weeks		Dermatologist	No		None	Malformation of the vermis cerebellum	Ongoing

* Diane-35 contains cyproteron acetate / ethinyl-estradiol, which is not indicated as an oral contraceptive, but has contraceptive properties.
** Contradicting information from initial contact and response letter
'yes': contraception was not adequately used

The inquiry on additional isotretinoin exposed pregnancies in their patient population (Q10) resulted in one additional pregnancy. However an explanation for the failure of the PPP could not be provided. In this additional case, also ultrasound examination showed malformation of the vermis of cerebellum was observed during ultrasound examination. This was not a duplicate case.

DISCUSSION

Nine out of the 17 questionnaires were completed, six were lost to follow-up and two were not returned. Most of the patients discontinued isotretinoin at gestational week 4-6. Pregnancy outcome was reported eight times, being four times spontaneous abortion, two times terminated pregnancy and two live born babies. One infant had congenital anomalies belonging to the retinoid embryopathy. Contraceptive measures reported consisted of not adequately performance by the patients or none were used. The responding HCPs, mainly gynaecologists, considered the communication about risk of isotretinoin exposed pregnancies and the measures to be taken 'good-excellent'.

Most of the women discontinued isotretinoin at gestational week 4-6, probably with the first positive pregnancy test or absence of menstruation. This might indicate that these women were aware that isotretinoin should not be taken while pregnant. The discontinuation of isotretinoin at this point in time might be reason for the high score on education of the risks of isotretinoin by the responding HCPs. Some HCPs even mentioned that the programme is adequate despite the occurrence of pregnancies during isotretinoin use.

Limitations of the study are the low number of exposures to draw conclusions. There might be under reporting of isotretinoin exposed pregnancies by HCPs contacting TIS for information on the teratogenicity of isotretinoin. Not all HCPs will contact TIS in case of isotretinoin exposure during pregnancy. The educational material on teratogenicity of isotretinoin is available for prescriber, pharmacist and patient. The HCPs contacting TIS were mainly gynaecologists and midwives, not prescribers and pharmacists who are the target groups of the educational material. On the other hand vitamin A derivatives, including isotretinoin, are on the market from 1973 onwards [11] and meanwhile HCPs will have gained knowledge on the teratogenicity of these drugs. Furthermore, gynaecologists and midwives are responsible for the pregnant woman and are not responsible for the compliance with a PPP, prescribers and pharmacists are. This might be the reason that information on contraceptive methods and adherence to these methods are poorly collected.

Table 2 Data available with Dutch Teratology Information Service at the moment of telephone intake, non-responders

Year	Age years	Period of exposure during pregnancy estimated from LMP*	Dose	Prescriber	Contraception Yes/no	Contraceptive method	Concomitant medication / recreational drugs	Ultrasound examination	Pregnancy outcome
2007		1 week before LMP – until 4 weeks	10 mg daily	abroad				Normal	
2008		Until 4 weeks	20 mg daily	GP				Pregnancy was not intact	Spontaneous abortion
2008	22	Until 4 weeks	30 mg daily		Yes	Nuvaring	Alcohol and cocaine	Empty amniotic cavity at 5th week	
2008		Until 4 weeks	20 mg twice daily	Dermatologist					
2009		9-12.5 weeks	-	Dermatologist					
2009		Until 4 weeks	40 mg daily		Yes	None adequate used			
2010		Until 5.5 weeks			Yes				
2011		Until 2 weeks			No				

* LMP: last menstrual period

Strengths of the study are the relatively high response rate, possibly because the questionnaire was sent with a personalised cover letter and that these HCPs had contacted TIS on these pregnancies. Therefore these HCPs considered the use of isotretinoin important and were willing to participate in the study.

Isotretinoin should be prescribed for a course of 16-24 weeks [12], implying that female patients should use adequate contraceptive measures for 24-32 weeks at least. In the cases presented, even this seems sometimes a problem. Regarding the fact that most of these pregnancies concerned women of the 25 years and older, this is worrisome. It is known from studies that adolescents and young adults might be less adherent to treatment [13,14], however this does not mean that the currently studied group would have full adherence to contraceptive measures.

A total of 17 pregnancies in a 5 year period seems a high number, especially with a programme to prevent pregnancies. A PPP is a risk minimisation measure to minimise the risk of congenital anomalies due to intra-uterine exposure of a certain drug by preventing pregnancies. The ultimate goal of a PPP is zero pregnancies. Taking into account the under reporting, the design and the implementation of the PPP should be reconsidered. Another aspect is the fact that the majority of the respondents reported that the education of the patients on consequences of isotretinoin exposure during pregnancy was excellent and even some of the respondents mentioned specifically that the programme had not failed. However, it might be possible that socially desirable answers were given. The questionnaires were sent to gynaecologists and midwives and their point of view of the PPP is different from the stakeholders of the PPP, such as prescribers of isotretinoin, pharmacists, patients and the health authorities. From surveys to dermatologists and pharmacists it is known that they mainly consider the patients responsible for compliance with contraceptive measures. The contacted HCPs in this survey focus on the aspect that women of childbearing potential should stop immediately isotretinoin intake at the moment the pregnancy test is positive. According to the point of view of these HCPs dealing with pregnant women and their pregnancy, the programme was adhered to.

The PPP recommend women of childbearing potential to use preferably two complimentary contraceptive methods but at least one method. In this study, information on contraceptive use was available for eleven patients of which six patients used an oral contraceptive, two patients used condoms, one patient had a NuvaRing® and two patients did not take contraceptive measures. Two patients who took an oral contraceptive had stopped during the first week after the last menstrual period and one patient had forgotten to take the pill twice. Based on this information and the fact that these patients were educated about the consequences of isotretinoin exposure during pregnancy, the lack of compliance contraceptive use is the weakest link. There have been several studies [15,16,17,18] on methods to improve adherence to contraceptive use in order to decline the number of unintended pregnancies, but to avoid pregnancies completely might only be possible by full compliance with contraceptive use. This might only be possible by using more permanent methods of contraception in combination with barrier methods instead of oral contraceptives.

Despite isotretinoin exposed pregnancies do occur, it seems that gynaecologists and midwives treating the pregnant women consider the education of patients treated with isotretinoin to be good. Patients were aware of the consequences of isotretinoin exposure during pregnancy and stopped at the moment of a positive pregnancy test, which is in adherence to the advice in the educational material and the product information. The pregnancies mainly followed poor compliance with contraceptive use or absence of contraceptive use, which might implicate that the focus to enhance the performance of the PPP should be on the compliance with contraceptive use.

ACKNOWLEDGEMENTS

No funding was received for the conduct of the study or preparation of the manuscript.
We would like to thank the participating health care professionals for their collaboration.

REFERENCES

1. Rosa F. Teratogenicity of isotretinoin. [letter] Lancet 1983; 322:513
2. Lammer E, Chen D, Hoar R, *et al*. Retinoic Acid Embryopathy. NEJM 1985; 313:837-41
3. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol 1992; 26:599-606
4. Adams J, Lammer EJ. The neurobehavioral teratology of isotretinoin. Reprod Toxicol 1993; 7:175-177
5. Crijns I, Straus S, Luteijn M, *et al*. Implementation of the harmonized EU isotretinoin Pregnancy Prevention Programme: a questionnaire survey among European regulatory agencies. Drug Saf 2012; 35:27-32
6. Autret-Leca E, Kreft-Jais C, Elefant E, *et al*. Isotretinoin exposure during pregnancy – Assessment of spontaneous reports in France. Drug Saf 2010; 33:659-65
7. De Santis M, Straface G, Cavaliere AF, *et al*. The need for restricted prescription of retinoid acid derivative isotretinoin to prevent retinoid teratogenicity. [letter] Prev Medicine 2007; 45:243-4
8. Schaefer Ch, Meister R, Weber-Schoendorfer C. Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. Arch Gynecol Obstet 2010; 281:221-7
9. Teichert M, Visser L, Dufour M, *et al*. Isotretinoin use and compliance with the Dutch Pregnancy Prevention Programme A retrospective cohort study in females of reproductive age using pharmacy dispensing data. Drug Saf 2010; 33:315-26
10. Crijns H, van Rein N, Gispen-de Wied C, *et al*. Prescriptive Contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study. Pharmacoepidemiol Drug Saf 2012 doi: 10.1002/pds.3200
11. Geiger JM, Baudin M, Saurat JH. Teratogenic risk with etretinate and acitretin treatment. Dermatology 1994; 189:109-16
12. Summary of Product Characteristics of isotretinoin: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Isotretinoin_29/WC500010881.pdf

13. Zaghoul SS, Cunlife WJ, Goodfield MJ. Objective assessment of compliance with treatments in acne. Br J Dermatol 2005;152:1015-21
14. Lott R, Taylor S, O'Niell J, Krowchik D, Feldman S. Medication adherence among acne patient: a review. J Cosmet Dermatol 2010; 9:160-6
15. Garbers S, Mesrve A, Kottke M, *et al*. Tailored health messaging improves contraceptive continuation and adherence: results from a randomized controlled trial. Contraception 2012 doi:10.1016/j.contracpetion.2012.02.005
16. Rajasekar D, Bigrigg A, Docherty G. Analysis of pill knowledge amongst oral contraceptive users in Scotland according to client characteristics. Eur J Contracept Reprod Health Care 1999;4:119-27
17. Hooper D. Attitudes, awareness, compliance and preferences among hormonal contraception users – a global, cross-sectional, self-administered, online survey. Clin Drug Investig 2010;30:749-63
18. Steinkellner A, Chen W, Denison S. Adherence to oral contraception in women on category X medications. Am J Med 2010;123:929-34

PART III